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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,631	04/11/2005	Seiichi Araki	T0509.70011US00	5167

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EXAMINER	
HUGHES, ALICIA R	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,631	ARAKI ET AL.	
	Examiner	Art Unit	
	ALICIA R. HUGHES	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2008*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims and Examination

Claims 15 and 19 are pending and the subject of this Office Action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 13 November 2006 has been entered.

Applicants' arguments filed on 09 January 2009 have been fully considered and are, in part, deemed to be persuasive regarding the previous rejection. Rejections not reiterated from this Office's previous action are hereby withdrawn. The rejections set forth herein constitute the complete set of rejections being applied to the instant application presently.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225

USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 15 and 19 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-20 of copending Application No. 10/472,621. This is a provisional double patenting rejection since the conflicting claims have not yet been patented. Applicants opt to delay their response until that realization of patentable subject matter by the Examiner.

In response, the arguments proffered in this Office's action of 27 August 2007 and 11 July 2008 are incorporated herein by reference in their entirety and the rejection is sustained for the reasons previously made of record.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grimble, et al as evidenced by Grimble II.

Applicant argues that the Grimble references merely teach glutathione as a major endogenous antioxidant and that riboflavin and vitamin B6 merely participate in glutathione status, but there is no direct correlation between glutathione or its production pathway, riboflavin and cytokine production and no teaching in the Grimble references that riboflavin prevents increased cytokine production.

The teachings of Grimble et al and Grimble II previously made of record are incorporated herein by reference in total. This Office's previous teachings of Grimble, et al and Grimble II in the Office Action of 27 August 2007 and 11 July 2008 are also incorporated herein by reference, in total.

As noted prior, Applicants argue that with regard to this Office's rejections made under 35 U.S.C. § 103(a): (1) the cited reference does not, in text or in diagram, teach or even suggest that riboflavin prevents increased cytokine production via the glutathione production pathway; and (2) the cited reference does not teach or suggest any relationship between riboflavin and cytokines. Examiner finds Applicants' responses wholly unpersuasive on both points based on the disclosures in Grimble, RF, "Effect of Antioxidative Vitamins on Immune Function with

Clinical Applications. International J. Vitam. Nutr. Res., Vol. 67, No. 5, pages 312-320 (1997)[hereinafter referred to as "Grimble, et al"][1] coupled with the state of the art at the time that the invention was disclosed. *Please see generally*, Grimble, Robert, "Modification of Inflammatory Aspects of Immune Function by Nutrients," Nutrition Research, Vol. 18, No. 7, pages 1297-1317 (1998)[hereinafter referred to as "Gimble II"]. Applicants further argue that the Examiner has reached her conclusion based on hindsight construction. Examiner respectfully disagrees.

At the time the present invention was disclosed, it was well-known in the art that there is a direct correlation between the functionality of balanced cytokine production when reacting to an inflammatory response and the activity of the glutathione production pathway to limit the creation of excessive cytokines (See Grimble II, page 1308, latter portion of Conclusion paragraph 3).[2] It has been known for quite some time that "[c]ytokines play a crucial role as modulatory agents by which the activity of the system is changed and metabolic activity of the host directed towards provision of nutrients for the system from endogenous sources. Nutrient intake, prior to infection will influence the extent of endogenous nutrient provision." *Id.* Glutathione is defined as a "major endogenous antioxidant," and "[v]itamin B_6 and riboflavin participate in the maintenance of glutathione status" (See Abstract). Thus, endogenous nutrient provision, i.e. glutathione production, controls hyperactivity of cytokines, or hypercytokinemia, and "[v]itamin B6 and riboflavin participate in the maintenance of glutathione status" (See Abstract).

[1] Previously cited on PTO-892 of 24 March 2006.
[2] The high priority given to combating pathogens is necessary because of the speed with which pathogens multiply once established within the host. In general terms, bacterial cells multiply at least 50 times as rapidly as T cells

In short, "[d]eficiencies in vitamins E, B_6 and riboflavin reduce cell numbers in lymphoid tissues of experimental animals and produce functional abnormalities in the cell mediated immune response." *Id*. Thus, where there is a deficiency in riboflavin, endogenous nutrient provision provided by glutathione will lack, thereby creating a heightened immune/inflammatory response that wields the over- or hyper-production of cytokines. Therefore, if a deficiency in riboflavin contributes to a heightened inflammatory response then it logically flows mechanistically that the presence of riboflavin has an inverse relationship with cytokine production as an immune response. It is the establishment of this relationship that makes the prior art rejection in Grimble, et al applicable to the instant invention.

Finally, Applicant has provided a declaration from Dr. Kohtaro Kodama. Examiner has closely examined the declaration, but on deciding the issue of whether the data therein indicates that vitamin B2 has no effect on glutathione levels in erythrocytes in LPS-treated rats and mice, the data is not conclusive and therefore, is unpersuasive. Specifically, LPS + Vitamin B2 showed a rise in glutathione concentration in rats (19.4 to 20.3) whereas LPS + Vitamin B2 showed a decrease in mice (17.4 to 15.8).

In view of the foregoing, the rejection is sustained.

Conclusion

No claims are allowed.

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under favorable conditions. Thus, the provision of nutrients to allow the immune system to function correctly cannot be left to chance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alicia Hughes whose telephone number is 571-272-6026. The examiner can normally be reached from 9:00 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR of Public PAIR. Status information for unpublished applications is available through Public PAIR only. For information about the PAIR system, see http://pair-direct-uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Raymond J Henley III/
Primary Examiner, Art Unit 1614

/Alicia Hughes/
Examiner, Art Unit 1614